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Subclinical synovitis detected by ultrasound in children affected by coeliac disease: a frequent manifestation improved by a gluten-free diet

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Abstract

Objective

Coeliac disease (CD) is a chronic autoimmune disease of the small intestine caused by the ingestion of gluten, in which musculoskeletal manifestations may occur. Aim of this study was to evaluate the prevalence and severity of joint involvement in paediatric patients with CD using musculoskeletal ultrasound (US).

Methods

Consecutive paediatric CD patients were enrolled and underwent US evaluations at level of knees, hips and ankles. The presence of joint effusion (JE), synovial hypertrophy, power Doppler signal and structural damage lesions (bone irregularities and erosions) was registered. Inflammatory abnormalities were scored on a semi-quantitative scale (0–3), and structural damage lesions on a dichotomous scale (0–1).

Results

Seventy-four CD children (mean age: 7.6 years; range: 1–14.2; M/F 24/50) were enrolled. Thirty-eight were on a gluten-containing diet (GCD) and 36 on a gluten-free diet (GFD). US showed the presence of abnormalities in 23 patients overall (31.1%); JE was the most frequently observed change (23/23). US abnormalities were observed in 19 patients (50.0%) of GCD group and in 4 of GFD group (11.1%, p=0.007). Interestingly, 12/23 (52.2%) patients with US-detected changes were asymptomatic.

Conclusion

This is the first US study demonstrating joint involvement in children with CD. JE, the most frequent manifestation, was present also in asymptomatic patients and was reduced in those on GFD. These findings may indicate that, also at joint level, an inflammatory response represented by the appearance of JE may be induced by exposure to gluten.

Key words

coeliac disease, ultrasound, subclinical synovitis

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Introduction

Coeliac disease (CD) is a chronic autoimmune disease of the small intestine caused by ingestion of gluten. In genetically susceptible individuals, carrying the DQA1*05-DQB1*02 or DQA1*03-DQB1*0302 alleles, the intestine exposure to gluten induces an inflammatory response, which leads to crypt hyperplasia and villous atrophy of the small bowel mucosa, pathological markers of the disease (1, 2). Based on published studies, the prevalence of the disease in the American and European population is approximately 1%. However, such prevalence could be underestimated because of those atypical or even silent forms which remain undiagnosed (3, 4). The classic form of CD in children consists of gastrointestinal symptoms (such as diarrhea or constipation, vomiting and abdominal pain); however, a number of cases is characterised by later-onset and atypical symptoms with extra-intestinal manifestations (5). In these patients, musculoskeletal manifestations, characterised by arthralgias, myopathies and non-erosive arthritis, may occur. To the best of our knowledge, at present data concerning the musculoskeletal involvement in children affected by CD are scarce (6-9). Both in adult and children pathology, musculoskeletal ultrasound (US) has played an increasing role in the assessment of patients with different rheumatic diseases, demonstrating its ability to detect a wide set of inflammatory and structural abnormalities (10-12). As for adults, the superiority of US over clinical examination in the detection of joint inflammatory status was demonstrated in children, allowing for the re-classification of oligoarticular on polyarticular disease subsets. Moreover, US allowed earlier assessment of cartilage and bone abnormalities than conventional radiology (13).

Based on the lack of data on the use of US in assessing patients with CD, the aim of the present study was to evaluate the prevalence and severity of joint involvement in a group of paediatric CD patients by using US. In addition, we compared the data obtained in the patient group on a gluten-containing diet (GCD) with those from the group on a gluten-free diet (GFD).

Methods

During a 22-month period (from May 2009 to March 2011), children affected by CD, referring to the Departmental Operative Unit "Celiachia e Patologie da Malassorbimento" of the Paediatric Department at Sapienza Università di Roma, were enrolled in our study. Specifically, we enrolled all children with a new diagnosis on GCD (group 1), and children with a previous diagnosis of CD, on a GFD for at least 6 months (group 2).

A history of injury in the previous 2 weeks and the presence of concomitant rheumatic diseases were considered exclusion criteria from the study.

Gastroenterological evaluation

At the time of diagnosis, all children performed laboratory analysis (total serum IgA [commercial kits]; IgA and IgG anti-endomisium antibodies [EMA, IFI on monkey esophagus]; IgA and IgG anti-transglutaminase antibodies [tTGAb; ELISA, Menarini, Firenze, Italy]) and underwent upper endoscopy (Olympus PQ20 or GIF-E, or GIF-P140 gastroscope), to obtain at least 2 samples from bulb mucosa and 4 from distal duodenum. The histological lesions of the small intestinal mucosa were evaluated according to the Marsh classification, as modified by Oberhuber *et al.* (14). The diagnosis of CD was performed according to the North American Society for Paediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) criteria (15).

Rheumatologic evaluation

The rheumatologic assessment was conducted at the Rheumatology Unit of the *Dipartimento di Medicina Interna e Specialità Mediche* - Sapienza University of Rome.

On the same day of the ultrasonographic examination, children were evaluated by a single rheumatologist who made the clinical history and performed physical examination. The medical history included registration of musculoskeletal symptoms, such as arthritis and/or arthralgia or limited motion, patient's sport activities, co-morbidities and familiarity for any rheumatic diseases and psoriasis. The

medical history included the registration of recent joint injures (*i.e.* accidental trauma). Physical examination included the analysis of joint tenderness, swelling and joints deformities, with focus particularly on the hip, knees and ankles joints. The rheumatologist was unaware of the type of diet followed by the patient.

Ultrasonographic assessment

US imaging was performed in all children, by using a Logiq 9 machine (General Electric, Medical Systems, Milwaukee, WI, USA), equipped with a 9–14 MHz linear array transducer, operating at 14 MHz frequency (gain 50%). In addition, for the evaluation of local pathological hypervascularisation, power Doppler (PD) was used, with the following settings: frequency 7.5 MHz, gain 50%, PRF 0.5 kHz.

According to the EULAR guidelines for US in rheumatology, in all children bilateral US evaluation of the hip, knee and ankle joints was performed by a single rheumatologist who was experienced in paediatric musculoskeletal US and was blinded to patients' laboratory and clinical features (16). The choice to evaluate these joints was in agreement with literature data, indicating that hip, knee and ankle are the most frequently involved in adult CD patients.

According to the international definitions currently in use, the presence of joint effusion (JE) and synovial hypertrophy (SH) was registered: JE was defined as an abnormal hypoechoic or anechoic intraarticular material that is displaceable and compressible, but does not exhibit Doppler signal; SH as an abnormal hypoechoic intraarticular tissue that is non-displaceable and poorly compressible and which may exhibit Doppler signal (17).

Moreover, we evaluated the bone profile, identifying the presence of bone irregularities (defined as loss of the continuous sharp hyper-echoic line of the bony cortex, with no evidence of erosion), and of erosions, defined as intra-articular discontinuities of the bone surface visible in 2 perpendicular planes (17). All abnormalities were scored on a 4-point semi-quantitative scale (0=absent; 1=mild; 2=moderate; 3=severe), except for bony cortex irregularities, which were scored on a dichotomous scale (present/absent). In addition, with the aim of assessing the intraobserver reliability, stored images of patients were re-evaluated by the same ultrasonographer 3 months after the end of the study.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences 13.0 (SPSS, Chicago, IL, USA) and GraphPad 5.0 (La Jolla, CA, USA). Normally distributed variables were summarised using the mean±SD, and non-normally distributed variables by the median and range. Wilcoxon's matched pairs test and paired *t*-test were performed. Univariate comparisons between nominal variables were calculated using chi-square (χ^2) test or Fisher test where appropriate.

The level of agreement, by using the Kappa Cohen coefficient**,** was defined as follows: ≤0.20 poor, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 good, and 0.81–1.00 almost perfect (18).

Two-tailed *p*-values were reported, while *p*-values less than or equal to 0.05 were considered significant. The local ethical committee approved the study, which was performed according to the Declaration of Helsinki criteria.

Results

Seventy-four children and adolescents (mean age: 7.6 years; range: 1-14.2; M/F 24/50) were enrolled. Thirty-eight children were classified for inclusion in group 1 and 34 in group 2.

Clinical, histological and US results are reported in Tables I and II. Children on GFD were older than those on GCD (9.2±6.7 *versus* 6.9±4.4; *p*=0.03). Patients in group 2, at the time of US assessment, had been assuming GFD for a period of 47.4±34.4 months. No other significant difference was found between the two groups of children regarding the clinical presentation of CD (typical, atypical or silent) (Table I). Among patients of group 1, all but one (97.3%) were positive for IgA tTGAb, and 34 out of the 37 patients (91.9%) tested positive for IgA EMA. Only 1 patient (0.03%) resulted to have a par-

Table I. Clinical, histological and US features of CD patients.

		GCD (n=38)	GFD (n=34)	*p*-value	GCD		*p*-value
					Children with US abnormalities (n=18)	Children without US abnormalities (n=20)	
Sex (M/F)	10/27	11/23	NS	6/12	5/15	NS	
Mean age±SD	6.9±4.4	9.2±6.7	0.03	7.5±4.1	6.2±4.6	NS	
CD Clinical form	Typical (n/%)	26/68.4	26/76.5	NS	12/66.6	16/80.0	NS
	Atypical (n/%)	4/10.5	3/8.8	NS	2/11.1	2/10.0	NS
	Silent (n/%)	6/15.8	5/14.7	NS	4/22.2	2/10.0	NS
Arthralgia, n/%	7/18.4	5/14.7	NS	6/33.3	1/5.0	0.02	
Diffusion of histological lesions[¥]	Diffuse (n/%)	34/91.9	30/88.2	NS	15/88.2[*]	19/95.0	NS
	Patchy (n/%)	1/ 2.7	0	NS	1/5.8[*]	0	NS
	Bulb (n/%)	2/ 5.4	0	NS	1/5.8=	1/5.0	NS

[¥]One patient in the GCD group and 4 patients in the GFD group could not be histologically characterised.
[*]One patient among children with US abnormalities had a potential CD.

tial IgA deficiency, and tested positive for both IgG tTGAb and IgG EMA. In group 2, all patients were antibody-negative. The demographic and clinical features of group 1 CD patients according to the presence of US abnormalities are reported in Table I.

US assessment showed the presence of at least one US abnormality in 23 CD patients (31.1%). JE present at any level (knee, hip or ankle) was the most frequent abnormality observed (23/23, 100% of patients with US involvement) and it was mild in all cases.

At least one US abnormality was observed in 19 (50.0%) children of group 1 and in 4 (11.1%) of group 2 (p=0.007). When evaluating the US-detected joint involvement, 36/228 joints (15.8%) showed at least one abnormality in children of group 1, compared to 5/216 (2.3%) of group 2 (p<0.0001). When considering the different joint sites, the most frequently involved joint was the knee (Table II, Fig. 1): 14/38 (36.8%) children of group 1 showed US abnormalities at knee level, compared to 4/36 of group 2 (11.1%). Mild JE was detected in 14 children (22 joints) of group 1 and in 4 (5 joints) children of group 2, with a significant difference between the two groups (p=0.01 when considering the number of children, p=0.005 when analysing the number of joints).

At the level of the hip joint, JE was the only detected abnormality and it was found in a higher percentage of children of group 1 compared with group 2 (5/38 patients [13.2%] - 7 joints, *versus* 0/36, [0%] p=0.02). No significant differences were detected when analysing the ankle joint. At this level, the only pathologic finding was JE, which was detected in 3/38 (7.9%) children (4 joints) of group 1 and in none (0%) of group 2. No significant association was found between the histological modifications or clinical presentation of CD and US abnormalities, when subgrouping the patients according with the presence of US abnormalities. Clinical evaluation demonstrated that 6/38 (15.8%) patients of group 1 and 5/36 (13.9%) of group 2 referred arthralgia, which was present only in patients who also had US-detected abnormalities.

Table II. US abnormalities detected in the knee joint.

US features	Patients			Joints		
	GCD n=38 (%)	GFD n=36 (%)	p-value	GCD n=76 (%)	GFD n=72 (%)	p-value
Total US abnormality	14 (36.8)	4 (11.1)	0.0005	22 (28.9)	5 (6.9)	0.0002
Synovitis						
JE (n/%)	14 (36.8)	4 (11.1)	0.0005	22 (28.9)	5 (6.9)	0.0002
SH (n/%)	3 (7.9)	0	NS	3 (3.9)	0	NS
PD (n/%)	1 (2.6)	0	NS	1 (1.3)	0	NS
Structural lesions						
Bone irregularities	0	0	NS	0	0	NS
Erosions	0	0	NS	0	0	NS

Finally, 12/23 (52.2%) of the patients with US detected abnormalities were asymptomatic.

No difference in terms of the severity of US detectable pathological findings was found between symptomatic and asymptomatic patients: in all the cases, the US alterations were classified as mild.

Intraobserver reproducibility assessment showed kappa's values of 0.8 and 1 for the SE and SH, respectively.

Discussion

To the best of our knowledge, this is the first ultrasonographic study focused on the analysis of joint involvement in children affected by CD. We demonstrated that US-detected joint abnormalities are more frequent in paediatric CD patients on GCD than in children on GFD, particularly with the evidence of subclinical joint effusion involving the knee. Musculoskeletal manifestations, characterised by arthralgia and non-erosive arthritis, with axial or peripheral asymmetrical involvement, can occur in patients affected by CD. Published studies about this topic, principally case reports or case series, documented a wide spectrum of musculoskeletal manifestations. Bourne *et al*. described 6 CD patients showing arthralgia, mainly involving shoulders, hips, knees and ankles (6). Interestingly, the onset of arthralgia preceded the diagnosis of CD and improved after starting GFD (6). More recently, two different reports separately have described clinical cases of silent CD presenting with unusual polyarthri-

Fig. 1. Suprapatellar scan of the knee: presence of mild synovial effusion (*) and hypertrophy (°). ^ epyphiseal plate.

tis (19, 20). Moreover, in 1996 Lubrano *et al*. evaluated musculoskeletal involvement in a large population of 200 adult patients with established CD. Twenty-six percent of these evaluated patients showed arthritis, presenting as an asymmetrical olygoarthritis in 36% of cases, affecting mainly shoulders, elbows, knees or ankles (21). Sacroileitis was detected in 29% of patients, generally unilateral (80%) (21). However, joint involvement has been evaluated only in adult CD patients and mainly by using clinical assessment and/or conventional radiography, so far.

In our study, we aimed at evaluating musculoskeletal involvement in a paediatric CD population through the use of US. This is an emerging imaging modality that has acquired an increasing role over the last years in the assessment and monitoring of rheumatic diseases (22, 23). US allows for a detailed depiction of the joint under investigation, providing information both on joint structures and peri-articular tissues (10). It has been mainly applied in adult patients, so far, for analysing various aspects of rheumatic diseases and its emerging role has been highlighted also in recently published classification criteria for specific disorders (24-29).

However, recently published studies have confirmed its relevant role also in the diagnosis and assessment of musculoskeletal disorders of childhood (13). The studies on the application of US in the assessment of joint involvement in children affected by juvenile idiopathic arthritis (JIA) demonstrated a greater sensitivity in identifying joint synovitis than clinical examination alone (30-33). Despite the increasing application of US in the evaluation of paediatric rheumatic diseases, some limitations are still present. In particular, data about the validity and reliability of US in the assessment of synovitis in JIA patients are missing (34). However, the assessment of musculo-skeletal US findings in children showed some difficulties. In particular, the physiologic modifications of structures in growing children and the presence of unossified immature skeleton could be misinterpreted as pathologic (35). Recently, a study conducted by Magni-Manzoni *et al*. has reported data about US assessment of 39 healthy children, showing the presence of US abnormalities on 35.9% of the cases (36). Specifically, SE was detected on 25.6% and SH on 12.8% of the enrolled children, in all the cases with a grade 1 (36). The results of the observation by Magni-Manzoni *et al*. could be explained by the application of the OMERACT definitions for RA adult patients and by the need of a clear understanding of normal US anatomy of children joint.

Our results confirmed that joint symptoms may be present in CD and that they are mainly represented by arthralgia. However, the present study shows that US has an added value over clinical examination, which is represented mainly by the possibility to detect abnormalities also in a relevant percentage of asymptomatic patients with CD. In these cases the most relevant finding was represented by the detection of JE, which is one of the components of synovitis. Particularly, US assessment demonstrated that joint abnormalities can occur in almost 1/3 of patients, with JE representing the most frequent US finding and the knee the most frequently involved joint compared with hips and ankles. In addition, our study pointed out that the prevalence of US abnormalities was significantly lower in children who started GFD than in those who were on a GCD. Therefore, these findings seem to confirm previous results and strengthen the hypothesis that GFD could improve extra-intestinal manifestations such as joint involvement (21).

In our patients, signs of structural changes were never detected, as demonstrated by the absence of erosions and bone surface irregularities. This particular aspect seems to confirm the previously described non-aggressive joint involvement in CD (6); however, further prospective studies are needed to deepen these complex aspects of disease.

The fact that we were able to identify subclinical synovitis by US supports the use of this imaging tool, being it more sensitive than physical examination in the detection of inflammatory joint abnormalities. This could be of value especially in paediatric patients, whose clinical examination could be sometimes difficult because of the poor compliance, the peculiar distribution of fat tissue and the difficulties in having definite anatomical landmarks. The evaluation of our data did not show any significant correlation between the US-detected abnormalities and histological features of CD. This result does not allow to identify a specific group of children with higher risk to develop musculoskeletal manifestations; however, an extensive joint US assessment may be recommended even in asymptomatic CD patients. Finally, US is non-invasive and well accepted by children modality, and could be the method of choice in the assessment of the inflammatory joint status in CD non-adult patients.

The present study showed some limitations. Particularly, the lack of inclusion of healthy controls and the absence of a consensus between at least two experienced ultrasonographers should be reported as a major limit. However, the good results in terms of intraobserver reliability improve the results that were obtained.

Conclusion

For the first time, we have shown that subclinical joint effusion is relatively frequent in children with CD and that GFD may reduce this manifestation. US may be considered a useful imaging tool for identifying CD patients with subclinical synovitis. Further perspective studies are needed to clarify these issues.

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